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NOVARTIS CORPORATE INTELLECTUAL PROPERTY ONE HEALTH PLAZA 104/3 EAST HANOVER, NJ 07936-1080				
EXAMINER				
ROYDS, LESLIE A				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

**Advisory Action
Before the Filing of an Appeal Brief**

Application No.

10/531,967

Applicant(s)

ALL-ERICSSON ET AL.

Examiner

Leslie A. Royds

Art Unit

1614

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 23 June 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because:
(a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
(b) ☐ They raise the issue of new matter (see NOTE below);
(c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
(d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: See Continuation Sheet (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
The status of the claim(s) is (or will be) as follows:
Claim(s) allowed: _____.
Claim(s) objected to: _____.
Claim(s) rejected: 1, 2 and 4-7.
Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____.
13. ☐ Other: _____.

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614

/Leslie A. Royds/
Patent Examiner, Art Unit 1614

Continuation of 3. NOTE:

Applicant's proposed after-final amendment filed June 23, 2008 will not be entered into the record because the proposed amendment to claim 1 raises a new issue that would require further consideration and/or search.

In particular, Applicant proposes amending present claim 1 to change the "dose" of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)-pyrimidin-2-ylamino] phenyl-benzamide to a "therapeutically effective dose" of the same. This proposed amendment clearly narrows the scope of the claimed subject matter to doses of the claimed active agent that are, in fact, therapeutically effective to treat the instantly claimed disease, whereas the previously pending claims allowed for the use of the active agent in any amount. In other words, further consideration of the presently applied art under 35 U.S.C. 103(a) would be required, as well as an additional assessment of the prior art to determine whether such an amendment would obviate the art of record and/or whether additional art would need to be applied.

Accordingly, the proposed claim amendments are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal because they raise new issues that require further consideration and/or search.

Continuation of 11. does NOT place the application in condition for allowance because:

Applicant's request for reconsideration of the present application with regard to the present application with regard to the present rejections under 35 U.S.C. 112, second paragraph, and 35 U.S.C. 103(a) in light of the amendments to the claims proposed and presented in the after-final amendment has been made. In light of the fact that the proposed amendments to the claims will not be entered into the record, Applicant's remarks directed to the obviation of these rejections as a result of the proposed amendments are not found persuasive.

For clarity of the record, Applicant's arguments pertaining to the previously pending set of claims is herein addressed.

Applicant traverses the instant rejection under 35 U.S.C. 103(a), stating that Mouriaux et al. teaches that the addition of SCF (c-kit ligand) to the medium did not change the melanocyte morphologies and did not induce proliferation in the absence of two other factors such that SCF was only determined to be mitogenic only in the presence of other factors. Applicant alleges that the disclosure of Mouriaux et al. does not lead one of skill in the art to expect that a c-kit inhibitor (i.e., imatinib) would be useful for uveal melanoma. Applicant argues that the combination of Zimmerman et al. and Ijland et al. provides for no more than a hypothesis that imatinib may be useful for uveal melanoma and that the skilled artisan would not have had a reasonable expectation of success without performing experiments to such an effect. Applicant further states that the proffered data is evidence of unexpected results, emphasizing that "it is reasonable to rely on data from the mesylate salt for the patentability of the full range of pharmaceutically acceptable salts" (p.4, Remarks). Applicant additionally emphasizes that "there is a clear effect in all cell lines at the high doses after 48 hours" and asserts that, in each of the cell lines tested, at least 75% of the cells die after 48 hours at the 5 and 10 micromolar concentrations and a clear dose response over all concentrations is seen in 2 cell lines.

Applicant's traversal has been fully and carefully considered, but fails to be persuasive.

Firstly, Applicant's traversal with regard to the application of Mouriaux et al. is unclear. Mouriaux et al. was cited solely for its teaching that activation of c-kit by its ligand was known to contribute to the proliferation of choroidal melanocytes, which are the cells involved in the pathogenesis of malignant melanoma of the eye and, therefore, one of skill in the art at the time of the invention would have reasonably expected that the uveal melanoma cells would have expressed c-kit.

The obviousness, however, of using the 4-(4-methylpiperazin-1-methyl)-N-[4-methyl-3-(4-pyrid-3-yl)pyrimidin-2-ylamino]phenylbenzamide for the treatment of uveal melanoma was not based upon the activity of this compound as a c-kit inhibitor. Rather, the asserted obviousness of using this active compound for treating uveal melanoma was based upon the fact that (1) Zimmerman clearly discloses the active compound as an effective inhibitor of the angiogenic effect of VEGF and (2) Ijland et al. clearly discloses that six different human primary uveal melanoma cell lines (32-1, Mel-202, OCM-1, OCM-3, OCM-8 and EOM-3) each demonstrated significant VEGF secretion, which was indicative of angiogenic potency and vessel proliferation for neovascularization and, thus, the use of a compound that clearly inhibits angiogenesis associated with VEGF for treating a disease that clearly exhibits angiogenesis as a result of significant VEGF secretion would have been prima facie obvious to one of ordinary skill in the art at the time of the invention. Such a person would have had a clearly reasonable expectation of success in treating uveal melanoma with such a compound because the inhibition of angiogenesis caused by VEGF expression would have inhibited the neovascularization necessary for tumoral growth.

In that line, Applicant opines that there is no reasonable expectation of success without performing experiments to such an effect. However, this is unpersuasive because Applicant is applying a standard of absolute predictability in order to find obviousness, which is not required. Rather, to find obviousness, only a reasonable expectation of success is required, which is provided supra and in the rationale provided in the previous Office Actions (to which Applicant's attention is directed). Please see MPEP Sect. 2143.02 and In re Rinehart, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976).

Secondly, Applicant's insistence that it is reasonable to rely upon data from the mesylate salt to predict the activity of other pharmaceutically acceptable salts is unpersuasive. Applicant advances no other specific reasons or evidence, aside from Counsel's own speculation, in support of this position. This assertion by Counsel is an unsupported allegation that the activity seen with the mesylate salt are predictive of the same activity of any or all other pharmaceutically acceptable salts. Statements of this nature are clearly unpersuasive in accordance with the guidance provided at MPEP §2145, which states, "The arguments of counsel cannot take the place of evidence in

the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997)".

Thirdly, Applicant again references the data provided in the instant specification as evidence of unexpected activity. However, Applicant's allegations that the present invention is non-obvious over the prior art because the use of the methanesulfonate salt of 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)-pyrimidin-2-ylamino]phenyl]-benzamide demonstrated an unexpected anti-proliferative effect in four uveal melanoma cell lines (OCM-1, OCM-3, UM 92-1 and mel 202) as reflected in the data presented in the Table at p.5 of the instant specification is again, as before, unpersuasive. While such results have been carefully and closely considered, it remains that (1) the compound used in the example was the methanesulfonate salt of 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)-pyrimidin-2-ylamino]phenyl]-benzamide, whereas the presently claimed subject matter is directed to the use of 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)-pyrimidin-2-ylamino]phenyl]-benzamide or any pharmaceutically acceptable salt thereof, and (2) several of the concentrations of methanesulfonate salt of 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)-pyrimidin-2-ylamino]phenyl]-benzamide, in fact, demonstrated an increase in cell proliferation in certain uveal melanoma cell lines and/or failed to demonstrate an unexpectedly potent anti-proliferative effect in the cell lines studied, whereas the presently claimed subject matter is directed to the use of any dose of 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)-pyrimidin-2-ylamino]phenyl]-benzamide or a pharmaceutically acceptable salt thereof. Furthermore, as evidenced by the data in the Table at p.5 of the specification, it appears that the dose and the amount of time that said dose of the compound is allowed to incubate with the uveal melanoma cells is clearly pertinent to achieving Applicant's allegedly unexpected anti-proliferative effect. Applicant fails to address these deficiencies in the remarks provided in the instant after-final submission to clarify how this data is commensurate in scope with the claimed subject matter and, thus, is representative of the same unexpected effects over the full scope of the claims. For these reasons, Applicant's remarks regarding the non-obviousness of the instant claims over the cited prior art are unpersuasive.

For these reasons set forth supra, the claims remain rejected for the reasons of record previously set forth in the final rejection of March 26, 2008, of which said reasons are herein incorporated by reference.

/Leslie A. Roysds/
Patent Examiner, Art Unit 1614